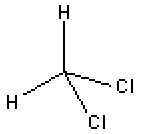
Methylene Chloride

CAS Registry Number: 75-9-2



I. Physical and Chemical Properties (HSDB, 1999)

Description	Colorless, volatile liquid
Molecular formula	CH_2Cl_2
Molecular weight	84.93
Air concentration conversion	1 ppm = 3.47 mg/m^3 @ 25^o C

II. Overview

The effects of methylene chloride have not been studied in children and there are no studies showing that exposure to methylene chloride *per se* differentially affects children. However methylene chloride is metabolized to carbon monoxide which is bound with higher affinity by fetal vs adult hemoglobin (affinity constant m = 213 vs 208; Di Cera *et al*., 1989). Thus the neurotoxic and cardiovascular effects of CO metabolically produced from methylene chloride following relatively high exposures may be exacerbated in fetuses and in infants with higher residual levels of fetal hemoglobin. Maternal exposure to high levels of CO during gestation has resulted in elevated levels of carboxyhemoglobin in the fetus and lowered birth weights in humans and animals. In animals, altered neurobehavioral adaptation has been attributed to prenatal maternal methylene chloride exposure. OEHHA's chronic Reference Exposure Level is based on significant elevation of carboxyhemoglobin (>2%; DiVincenzo and Kaplan, 1981) in humans exposed occupationally with a LOAEL of 40 ppm (14 ppm time adjusted to a 24 hour day). It includes an intraspecies uncertainty factor of 10 and a LOAEL uncertainty factor of 10 for a total uncertainty factor of 100. It should be noted that typical ambient concentrations are almost three orders of magnitude lower than our chronic REL.

Methylene chloride vapors are heavier than air (vapor density = 2.93) and tend to concentrate near the ground. Because of their shorter stature, children may be more at risk of exposure than adults during accidental spills or through the use of methylene chloride in unventilated areas. The higher ventilation rates in children compared to adults mean that children may receive a higher dose of methylene chloride than adults during inhalation exposures.

III. Principal Sources of Exposure

Methylene chloride is used in paint and varnish remover, in aerosols as a co-solvent or vapor pressure depressant, and in solvent degreasing and metal cleaning. It is used in plastics processing and in

extraction of fats and oils from food products. The removal of methylene chloride from such consumer products as hair sprays and some paint removers has reduced the opportunity for non-occupational exposure. Statewide median and maximal monitored ambient concentrations were 0.50 and 4.8 ppb in 1999. Of 16,332,000 lbs released in California in 2000, 5,350,000 lbs were in Los Angeles County (CARB, 2001). In the South Coast Air Basin, the range of median and maximal values in 1999 were 0.5-1.1 and 1.4-4.5 ppb, respectively, as reported by the California Ambient Toxics Monitoring Network (CARB, 1999).

IV. Potential for Differential Effects

A. Summary of Key Human Studies

To study the biotransformation of inhaled methylene chloride, COHb formation was measured in the blood of eleven resting non-smokers following methylene chloride exposure to 50, 100, 150 and 200 ppm methylene chloride for 7.5 hrs on 5 consecutive days. All exposure levels produced elevated COHb and CO in exhaled air. The peak blood COHb saturation was 1.9, 3.4, 5.3, and 6.8%, respectively, for the 50, 100, 150, and 200 ppm groups (DiVincenzo and Kaplan, 1981).

Low birth weights have been associated with maternal exposure to elevated CO during the last trimester. Exposure to >5.5 ppm of CO during the last trimester of pregnancy was associated with an increased risk of low birth weight (odds ratio 1.22, 95% CI 1.03-1.44) among 125,573 children born to women living in Los Angeles (Ritz and Yu, 1999). It is important to note that COHb was not determined in mothers or newborns and CO was only one of numerous air pollutants to which the mothers were exposed.

Similarly Koren *et al*. (1991) studied the effects of CO poisoning from various sources (including from exposure to methylene chloride) during gestation on pregnancy outcomes in 38 women. There was a significant association ($p<0.001$) between severe maternal CO toxicity and adverse pregnancy outcomes including cerebral palsy. While this study underscores the potential impact of CO poisoning during pregnancy, the specific outcomes of the three methylene chloride exposures were not reported.

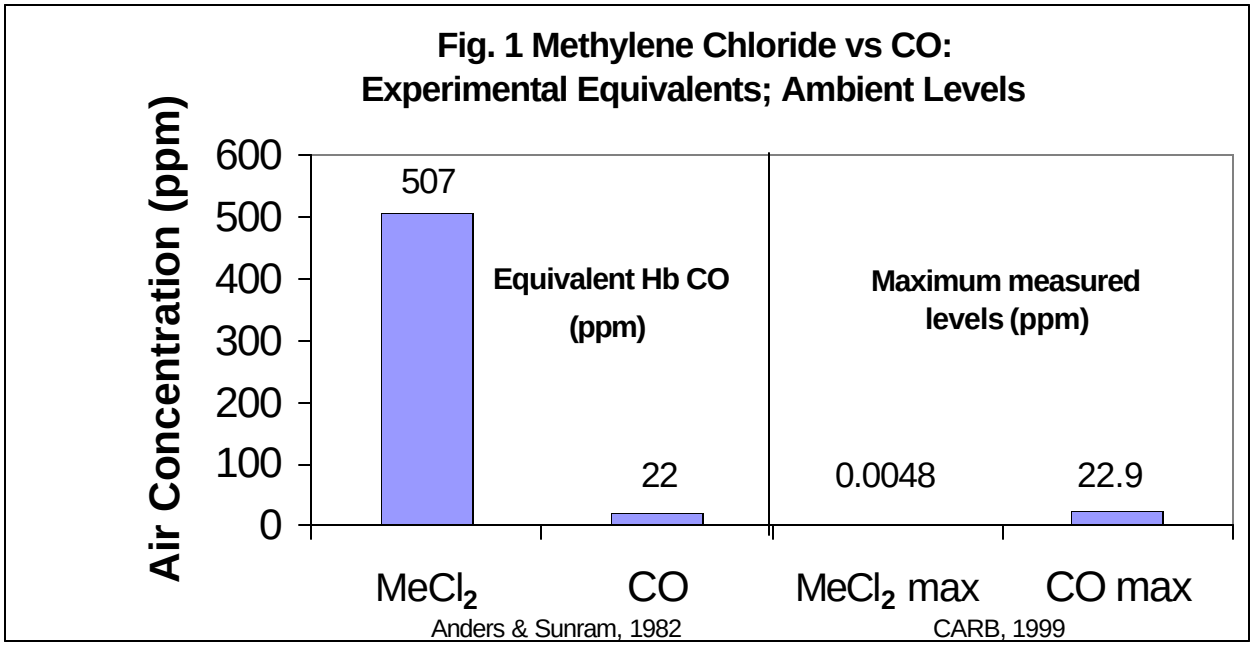
The information on potential developmental effects in humans is limited. A retrospective study of female pharmaceutical workers exposed to a variety of organic solvents indicated that solvent exposure, and particularly methylene chloride exposure, resulted in an increase in spontaneous abortions (Taskinen *et al*., 1986). In all, 1,795 pregnancies were followed with 142 spontaneous abortions occurring. The odds ratio for methylene chloride exposure was 1.0 to 5.7 (average = 2.3; $p<0.06$). There was a significant effect of exposure to four or more solvents compared with age-matched controls ($p<0.05$). The concentrations of methylene chloride were not reported in the study.

B. Summary of Key Animal Studies

No studies were identified which provided evidence of differential susceptibility from postnatal exposures of young animals to methylene chloride. However there is some suggestion that gestational exposure to very high levels may result in persistent neurobehavioral alterations in the offspring.

Bornschein *et al*. (1980) exposed rats before and/or during pregnancy to 0 and 4500 ppm methylene chloride. The exposed pups showed significantly slower rates of behavioral habituation to novel environments at 10 and 15 days of age ($p<0.01$). By 150 days of age, exposed male rats still demonstrated significantly altered activity levels compared to controls ($p<0.02$). In this exploratory study, levels of carboxyhemoglobin were not determined to distinguish the effects of CO versus the parent compound, methylene chloride.

Anders and Sunram (1982) exposed pregnant rats (gestation day 21) to methylene chloride at 507 ppm or CO at 22 ppm for 1 hour and monitored the fetal and maternal blood concentrations of methylene chloride and/or CO. Exposure to 22 ppm CO gave approximately the same fetal blood CO levels as those achieved following the 23-fold higher exposure to methylene chloride at 507 ppm (157 vs 160 nmol/ml) (Fig. 1). Whereas the level of methylene chloride in fetal blood was significantly lower than in maternal blood, the levels of fetal CO were comparable to maternal CO and thought to be due to equilibration of CO between maternal and fetal circulation.



V. Additional Information

A. Other Toxicity

Methylene chloride is rapidly absorbed through the lungs into the systemic circulation and excreted via the lungs in exhaled air. At high concentrations most of the absorbed methylene chloride is exhaled unchanged with the remainder metabolized to carbon monoxide (CO), carbon dioxide (CO_2) and inorganic chloride. The main toxic effects of methylene chloride are reversible central nervous system (CNS) depression and carboxyhemoglobin (COHb) formation. The neurotoxicity of methylene chloride

is thought to be related to its lipophilicity, which allows it to enter nerve cell membranes and interfere with signal propagation, and to the hypoxia associated with the formation of COHb. COHb formation above 2% is considered the critical effect in humans. In addition to the CNS, the liver, heart, kidneys and lungs may be adversely affected at high doses.

The health effects of methylene chloride derive from the lipophilicity of the parent compound and the toxicity of its metabolites, formaldehyde and CO. The available data suggest that there are two pathways by which methylene chloride is metabolized. One pathway utilizes cytochrome P-450 2E1 (CYP2E1) and produces CO and CO_2. The second involves glutathione transferase T1-1 (GSTT1-1) and leads via formaldehyde to CO_2 (Mainwaring *et al*., 1996). However, at low exposure levels methylene chloride is thought to be metabolized predominately by the P-450s to CO (Stewart *et al*., 1972).

B. Regulatory Background

The acute inhalation reference exposure level is 14,000 $\mu g/m^3$ and a chronic inhalation reference exposure level of 400 $\mu g/m^3$ (100 ppb) was developed (OEHHA, 2000) based on occupational exposure (DiVincenzo and Kaplan, 1981). Methylene chloride is classified as a probable human carcinogen (B2) based on sufficient evidence of carcinogenicity in animals and inadequate human data. The cancer inhalation unit risk was established at 1 $x10^{-6}$ $(\mu g/m^3)^{-1}$ by the California Department of Health Services (CDHS, 1987).

VI. Conclusions

Methylene chloride is metabolized to carbon monoxide, which has a higher affinity for fetal hemoglobin than adult hemoglobin. This is therefore a basis for differential toxicity beween infants and adults. The chronic Reference Exposure Level (cREL) OEHHA developed for methylene chloride is based on the formation of carboxyhemoglobin in adults. The ratio of the ambient air concentrations (statewide average) to the cREL is 0.005. Thus, general exposures are well-below levels that would result in significant carboxyhemoglobin formation even in the neonate. Thus, OEHHA has placed methylene chloride in Tier 2. There are, however, significant emissions statewide of methylene chloride from facilities in the Air Toxics Hot Spots program, and so local concentrations may be higher than the statewide average. Should information indicating locally significant concentrations become available, OEHHA may revisit listing methylene chloride under SB 25.

VII. References

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